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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/866,296	05/25/2001	Eugene A. Woltering	98M006.1 Woltering	4311

25547 7590 11/19/2002

PATENT DEPARTMENT
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EXAMINER	
AFREMOVA, VERA	
ART UNIT	**PAPER NUMBER**
1651	10

DATE MAILED: 11/19/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.	Applicant(s)
09/866,296	Woltering et al.
Examiner	**Art Unit**
Vera Afremova	1651

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) X Responsive to communication(s) filed on *Aug 26, 2002*.

2a) X This action is **FINAL.** 2b) ☐ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) X Claim(s) *1-37* is/are pending in the application.

4a) Of the above, claim(s) *14-37* is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) X Claim(s) *1-13* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are a) ☐ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1. ☐ Notice of References Cited (PTO-892)
2. ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3. ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s).
4. ☐ Interview Summary (PTO-413) Paper No(s).
5. ☐ Notice of Informal Patent Application (PTO-152)
6. ☐ Other

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DETAILED ACTION

Claims 1-13 as amended are under examination in the instant office action [Paper No. 8 filed 8/26/2002].

Claims 14-37 have been withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to nonelected inventions. Election was made without traverse [Paper No. 6 filed 6/12/2002].

In response to the applicants' request to clarify the grouping of claims 14-23, 25 and 27-37, it is noted that these claims were/are considered in the instant prosecution as claims of the non-elected Group II.

Information Disclosure Statement

The information disclosure statement filed 8/26/2002 fails to comply with 37 CFR 1.98(a)(3) because it does not include a concise explanation of the relevance, as it is presently understood by the individual designated in 37 CFR 1.56© most knowledgeable about the content of the information, of each patent listed that is not in the English language. It has been placed in the application file, but the information referred to therein has not been considered.

The relevance of application 09/196,259 is uncertain particularly in view that this application is a patent now but the applicants' form PTO-1449 refers to the application. With regard to two other documents by Gulec et al., it is noted that they are not copies of published and/or publicly available documents and that there is no any reference to the source and publication date of these

documents on the applicants' form PTO-1449, and, thus, the relevance of these documents as a prior art is uncertain as submitted by applicants.

Response to Arguments

Applicant's arguments filed 8/26/2002 have been fully considered but they are not persuasive for the reasons below.

Claim Rejections - 35 USC § 112

Claims 1-13 remain rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention as explained in the prior office action and for the reasons below.

Claim 1 remains indefinite with respect to the "if any" as explained in the prior office action. Applicants appears to argue that one of ordinary skill in the art would understand this limitation (response page 4, par. 3). Yet, the claim does not indicate what is a "time sufficient" to incubate and to observe the tissue in order to demonstrate the fact that there is no growth of angiogenic vessels as argued. Is it a day, a month or a year, for example?

Claim 2 remains indefinite with respect to the phrase "substantially" as explained in the prior office action. Applicants appears to argue that the term "substantially" is often definite depending on context (response page 4, last par. 3). Yet, neither specification nor claims provide particular definitions of amounts which are included or excluded by the phrase "substantially"

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Claim Rejections - 35 USC § 102

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claims 1-4, 6-10 and 13 remain rejected under 35 U.S.C. 102(b) as being anticipated by US 5,856,184 [A] as explained in the prior office action and for the reasons below.

Claims are directed to a method for assaying angiogenesis *ex vivo* wherein the method comprises step of embedding a three-dimensional tissue sample in a matrix, step of supplying the embedded tissue sample with a medium that supports growth of the tissue sample, step of incubating the embedded tissue sample in the medium for a time sufficient to allow angiogenic vessels to growth into the matrix surrounding the tissue sample and step of observing or measuring the angiogenic vessels. Some claims are further drawn to the use of medium supplemented with serum and/or various factors which enhance or suppress angiogenesis. Some claims are further drawn to the use of matrix such as fibrin, collagen, agar, or Matrigel. Some claims are further drawn to the use of various tissues in the method for assaying angiogenesis.

The cited patent is relied upon as explained in the prior office action and repeated herein.

US 5,856,184 [A] discloses a method for assaying angiogenesis ex vivo wherein the method comprises step of embedding three-dimensional tissue samples of aorta segments in the Matrigel matrix, step of supplying the embedded tissue samples with a medium that supports growth of the tissue samples or with MCDB medium, step of incubating the embedded tissue samples in the medium for a time sufficient to allow angiogenic vessels to growth into the matrix

surrounding the tissue samples and step of observing or measuring the angiogenic vessels (col. 11, lines 15-40). The commercial Matrigel product contains fibrin, collagen, gelatin, agar or agarose. Although the cited patent is silent with regard to the presence or absence of serum in the commercial medium MCDB, it teaches the use of the three-dimensional system for observing and measuring differences in angiogenesis as the result of addition of various factors in the medium that supports growth such as various collagen fractions, for example. And , thus, the cited method is considered to anticipate the presently claimed invention to the extend of using unidentified exogenous factors whether they are derived from serum or not as encompassed by the claims 2, 3 or 13.

With regard to the cited patent US 5,856,184 [A] applicants argue (response page 9, par. 4) that a segment of the thoracic aorta of mouse is not a "three-dimensional" system within the scope of the present invention since the applicants' definitions exclude the use of vein and artery (specification page 29, lines 5-6). In response to applicant's argument that the cited patent fails to show certain features of applicant's invention, it is noted that the features upon which applicant relies are not recited in the rejected claims. Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993).

Claims 1-6 and 13 are rejected under 35 U.S.C. 102(b) as being anticipated by Brown et al. [U] as explained in the prior office action and for the reasons below.

Claims are directed to a method for assaying angiogenesis *ex vivo* wherein the method comprises step of embedding a three-dimensional tissue sample in a matrix, step of supplying the embedded tissue sample with a medium that supports the growth of the tissue sample, step of incubating the embedded tissue sample in the medium for a time sufficient to allow angiogenic vessels to growth into the matrix surrounding the tissue sample and step of observing or measuring the angiogenic vessels. Some claims are further drawn to the use of medium with or without serum, to the use of medium supplemented with various factors including vascular endothelial growth factor (VEGF) or fibroblast growth factor (FGF) for observing differences in angiogenesis in various systems. Some claims are further drawn to the use of matrix such as fibrin.

The cited reference by Brown et al. [U] is relied upon as explained in the prior office action and repeated herein.

Brown et al. [U] teaches a method for assaying angiogenesis *ex vivo* wherein the method comprises step of embedding three-dimensional tissue sample such as human placental blood vessel fragments a fibrin matrix, step of supplying the embedded tissues sample with a medium that supports the growth of the tissue sample, step of incubating the embedded tissue sample in the medium for a time sufficient to allow angiogenic vessels to growth into the matrix surrounding the tissue sample and step of observing or measuring the angiogenic vessels as the result of addition of various factors including vascular endothelial growth factor (VEGF), fibroblast growth factor (FGF) in the presence or absence of serum (see abstract and page 551,

col. 1, lines 4-20). The cited reference anticipates all active steps and all structural elements of the presently claimed method.

With regard to the cited reference by Brown et al. applicants appear to argue (response page 9, last par.) that the 1-2 m mammalian tissue segments including blood vessels derived from the surface of human placenta are not a "three-dimensional" system within the scope of the present invention. No definitions with regard to a size of mammalian tissues sample is found in the specification. Moreover, the features upon which applicants relie, such as either size or blood vessels, are not recited in the rejected claims. Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993).

Claims 1, 3, 4, 6, 7, 12 and 13 are rejected under 35 U.S.C. 102(b) as being anticipated by Montesano et al. [V] as explained in the prior office action and for the reasons below.

Claims are directed to a method for assaying angiogenesis *ex vivo* wherein the method comprises step of embedding a three-dimensional tissue sample in a matrix, step of supplying the embedded tissue sample with a medium that supports the growth of the tissue sample, step of incubating the embedded tissue sample in the medium for a time sufficient to allow angiogenic vessels to growth into the matrix surrounding the tissue sample and step of observing or measuring the angiogenic vessels. Some claims are further drawn to the use of medium supplemented with serum and/or with various factors which enhance or suppress angiogenesis.

Some claims are further drawn to the use of matrix such as fibrin or collagen. Some claims are further drawn to the use of various tissues excluding tumor fragments and segments of artery or vein.

The cited reference by Montesano et al. [V] is relied upon as explained in the prior office action and repeated herein.

Montesano et al. [V] discloses a method for assaying angiogenesis *ex vivo* wherein the method comprises step of embedding three-dimensional tissue samples of muscular and adipose tissues in a matrix of fibrin gel or collagen gel, step of supplying the embedded tissue samples with a medium that supports the growth of the tissue samples or MEM medium with serum, step of incubating the embedded tissue samples in the medium for a time sufficient to allow angiogenic vessels to growth into the matrix surrounding the tissue samples and step of observing or measuring the angiogenic vessels (see abstract, page 807 at section "Materials and Methods" and figures 1-2). The cited reference anticipates all active steps and all structural elements of the presently claimed method.

With regard to the cited reference by Montesano et al. applicants appear to argue (response page 10, par. 1) that the small fragments of mammalian tissue or fragments agglomerates smaller than a drop of saline are not a "three-dimensional" system within the scope of the present invention. No definitions with regard to a size of mammalian tissues sample is found in the specification. Moreover, the features upon which applicants relie are not recited in the rejected claims. Although the claims are interpreted in light of the specification, limitations

from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993). Moreover, the muscular and adipose tissues explants of Montesano et al. are clearly taught as an effective model for assaying angiogenesis *in vitro* or *ex vivo* (abstract) and, thus, whatever sizes of fragments were used, they were sufficiently large to function as an angiogenesis model within the scope of the present invention excluding an isolated vein or an isolated artery.

Claims 1, 4, 11 and 13 are rejected under 35 U.S.C. 102(b) as being anticipated by Lugassy et al. [W] as explained in the prior office action and for the reasons below.

Claims are directed to a method for assaying angiogenesis *ex vivo* wherein the method comprises step of embedding three-dimensional tissue sample in a matrix, step of supplying the embedded tissue sample with a medium that supports growth of the tissue sample, step of incubating the embedded tissue sample in the medium for a time sufficient to allow angiogenic vessels to growth into the matrix surrounding the tissue sample and step of observing or measuring the angiogenic vessels. Some claims are further drawn to the use of medium supplemented various factors which enhance or suppress angiogenesis. Some claims are further drawn to the use of various tissues in the method for assaying angiogenesis including tumor tissues.

The cited reference by Lugassy et al. [W] is relied upon as explained in the prior office action and repeated herein.

Lugassy et al. [W] discloses a method for assaying angiogenesis *ex vivo* wherein the method comprises step of embedding three-dimensional tissue sample such as angioma or tumor fragments a matrix, step of supplying the embedded tissue samples with a medium that supports growth of the tissue samples, step of incubating the embedded tissue samples in the medium for a time sufficient to allow angiogenic vessels to growth into the matrix surrounding the tissue samples and step of observing or measuring the angiogenic vessels. The cited reference teaches that the disclosed three-dimensional *in vitro* or *ex vivo* tumor system allows for observing angiogenesis in malignant samples and production of metastases. Thus, the cited reference anticipates the presently invention as claimed and as intended.

With regard to the cited reference by Lugassy et al. [W] applicants appear to argue (response page 10, par. 2) that the mammalian tumor tissue of the cited reference is a "rebuilt" tumor model obtained from isolated cells and that it is not a "three-dimensional" system within the scope of the present invention. Although the specification definitions might be considered as excluding tumor cell agglomerates without vascularization (page 29, lines 5-10), the claimed invention allows for the absence of angiogenic vessels by the virtue of phrase "if any" (claim 1) and the claimed invention does not indicate any nature of a tumor fragment (claim 11). Moreover, the tumor model of Lugassy et al. comprises cells of vascular origin (page 38, line 17) within the scope of the present invention.

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Claim Rejections - 35 USC § 103

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claims 1-13 remain rejected under 35 U.S.C. 103(a) as being unpatentable over US 5,856,184 [A] taken with Brown et al. [U], Montesano et al. [V] and Lugassy et al. [W] as explained in the prior office action and for the reasons below.

Claims are directed to a method for assaying angiogenesis *ex vivo* wherein the method comprises step of embedding a three-dimensional tissue sample in a matrix, step of supplying the embedded tissue sample with a medium that supports growth of the tissue sample, step of incubating the embedded tissue sample in the medium for a time sufficient to allow angiogenic vessels to growth into the matrix surrounding the tissue sample and step of observing or measuring the angiogenic vessels. Some claims are further drawn to the use of medium supplemented with serum and/or various factors which enhance or suppress angiogenesis. Some claims are further drawn to the use of matrix such as fibrin, collagen, agar, or Matrigel. Some claims are further drawn to the use of various tissues in the method for assaying angiogenesis including or excluding tumor or artery or vein fragments.

The cited references are relied upon as explained in the prior office action and repeated herein.

All cited references teach methods for assaying angiogenesis *ex vivo* as the presently claimed wherein the cited methods encompass the use of three-dimensional systems comprising

tissue samples embedded into various matrix and supplied with various media supplemented with various growth factors which enhance or suppress angiogenesis as required by the presently claimed. All cited references teach the disclosed systems as models for *ex vivo* measuring, observing and assaying angiogenesis. Some cited references demonstrate the use of tissue samples including artery or vein fragments in the methods for assaying angiogenesis as required by the claimed method, for example: US 5,856,184 [A] and Brown et al. [U]. The other references demonstrate the use of tissue samples either excluding tumor, artery or vein fragments {Montesano et al. [V]} or including tumor fragments {Lugassy et al. [W]} as required by the presently claimed method.

Therefore, it would have been obvious to one having ordinary skill in the art at the time the claimed invention was made to practice the method for assaying angiogenesis *ex vivo* as the presently claimed with a reasonable expectation of success in observing angiogenesis in various tissue samples including that which are claimed because the prior art references teach the identical three-dimensional ex vivo systems and suggest the use of various factors which enhance or suppress angiogenesis. Thus, one of skill in the art would have been motivated to use the three-dimensional ex vivo systems for the benefit of studying angiogenesis in various tissues. Thus, the claimed invention as a whole was clearly prima facie obvious, especially in the absence of evidence to the contrary. The claimed subject matter fails to patentably distinguish over the state art as represented be the cited references. Therefore, the claims are properly rejected under 35 USC § 103.

With regard to the claim rejection under 35 USC § 103 applicants' arguments (page 11, par. 2) fail to comply with 37 CFR 1.111(b) because they amount to a general allegation that the claims define a patentable invention without specifically pointing out how the language of the claims patentably distinguishes them from the references.

No claims are allowed.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

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Any inquiry concerning this communication or earlier communications from the examiner should be directed to Vera Afremova whose telephone number is (703) 308-9351. The examiner can normally be reached on Monday to Friday from 9:00 to 5:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Wityshyn, can be reached on (703) 308-4743. The fax phone number for this Group is (703) 308-4242.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Vera Afremova,

Art Unit 1651

November 12, 2002.

Application/Control Number: 09/866,296

Art Unit: 1651

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Vera Afremova,

Art Unit 1651

November 12, 2002.

Irene Marx

IRENE MARX
PRIMARY EXAMINER